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THE SEED AND THE SOIL: EFFECT OF DOSAGE, PERSONALITY AND STARTING STATE ON THE RESPONSE TO Δ^9TETRAHYDROCANNABINOL IN MAN

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1 The effects of two doses of Δ^9THC (2.5 and 10 mg), delivered by paced smoking of herbal cigarettes, on CNV magnitude, subjective mood ratings and heart rate were studied in 20 subjects.

2 There were highly significant interactions between drug dosage and Extraversion and Neuroticism scores, so that the direction and degree of response to the different doses of Δ^9THC depended on the personality characteristics of the subjects.

3 The effects of 8 mg Δ^9THC and placebo, delivered in herbal cigarettes smoked naturally, on smoking behaviour, subjective mood ratings, measures of autonomic activity and auditory and visual cortical evoked responses were compared in 12 subjects.

4 Smoking behaviour, subjective 'high' rating and elevation of heart rates were the most significant discriminators between drug and placebo. The latency of some of the components of the visual evoked responses was also increased by Δ^9THC.

5 There was a significant correlation between the effects of Δ^9THC on skin conductance reactivity and the basal (pre-drug) level, reactivity increasing after drug in subjects with low basal reactivity and decreasing in those with high basal levels.

6 Both experiments provided clear evidence of dose-dependent biphasic stimulant and depressant actions of Δ^9THC on both subjective and objective measures, and these effects were influenced by the personality and the starting state of the subjects.

Introduction

Cannabis produces a number of physiological and psychological effects in man which vary according to dosage, mode of administration, setting, expectations and personality of the taker (Paton & Pertwee, 1973; Tart, 1970; Jones, 1971). In this respect, cannabis does not differ from many other commonly used psychotropic drugs such as nicotine, benzodiazepines and amphetamines for which dose-dependent, biphasic, stimulant and depressant effects on various measures of central nervous system activity have been described (Ashton *et al.*, 1974, 1976; Ashton *et al.*, 1978a; Kopell *et al.*, 1974). Interactions of centrally acting drugs with personality (Eysenck, 1967; Eysenck & O'Connor, 1979) and with environmental setting (Schachter, 1971; Bem, 1972) are also well known. However, the extent to which the characteristics of the 'soil' can influence both the degree and direction of response to the 'seed' (a centrally acting drug), and the extent to which bidirectional changes between and within subjects to different doses of 'seed' can mask an overall drug response are perhaps not generally appreciated. In this paper, some of the complex interactions of dosage, personality and starting state with subjective and autonomic effects, effects on cortical evoked responses and on performance are further explored with reference to Δ^9-tetrahydrocannabinol (Δ^9THC), one of the main active principles of cannabis.

Methods

Drugs

Δ^9THC dissolved in alcohol solution was obtained from the National Institute of Mental Health, Washington, D.C. Herbal cigarettes (Taunton), devoid of nicotine, were spiked with 2.5 mg, 8 mg or 10 mg of Δ^9THC by a spiking machine (Hazleton Laboratories, Harrogate, England), which ensured an even distribution along the length of the cigarette.

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Between sessions the cigarettes were stored at 2°C in containers flushed with nitrogen to prevent oxidation. Placebo cigarettes were prepared by blotting unspiked Taunton cigarettes with alcohol and re-drying to produce an identical appearance with the spiked cigarettes. There was little or no difference in taste or smell between the spiked and the placebo cigarettes owing to the strong 'grass-like' smell of the herbal cigarettes. A Home Office Licence was granted for use of Δ^9THC on human subjects on the premises.

Subjects

Subjects were all young, healthy unpaid volunteers recruited by word of mouth. A pilot study indicated that frequent users of cannabis respond to Δ^9THC differently from occasional users, as measured by several of the variables used in this study. Therefore subjects were selected on the basis of light to moderate use of cannabis (once a week or less often) and non-usage of 'hard' drugs. Two separate experiments were conducted on different subjects: 20 subjects (12 males and 8 females, mean age 23.2 years) took part in Experiment 1 and 12 subjects (8 male and 4 female, mean age 23.7 years) in Experiment 2. Ethical permission was obtained from the appropriate committee.

Measures

1. *Electroencephalographic responses*

(a) Contingent negative variation (CNV) with reaction time (RT) was measured as previously described (Ashton *et al.*, 1974, 1976) with compensation for artefacts due to eye movements (Ashton *et al.*, 1978a). Briefly, subjects were presented with a short warning tone, S_1 (1000 Hz, 7 ms duration) followed by a longer tone, the imperative stimulus, S_2 (650 Hz, 400 ms duration) to which they responded by pressing a button. The time from S_2 to the response was recorded as reaction time. The interval between successive S_1, S_2 pairs was varied randomly between 12 and 16 s. Three different S_1–S_2 intervals (2, 3, and 4 s) were used; these were presented in randomised order, each series consisting of 26 signal pairs: 8 of 2 s, 8 of 3 s, and 10 of 4 s S_1–S_2 intervals. The EEG signal was stored on magnetic tape (Racal 4 tape recorder) and the records of the CNV for each of the S_1–S_2 intervals subsequently averaged separately by a PDP8/E computer. CNV magnitude, measured by the computer, was expressed in μVs as previously described (Ashton *et al.*, 1974).

(b) Visual evoked response (VER) and auditory evoked response (AER) were recorded from silver/silver chloride electrodes between vertex and linked mastoid positions, with an earth electrode on the forehead. Eye movement artefacts were compensated as for the CNV. The EEG signals were amplified with a high gain AC amplifier, fed into a PDP8/E computer programmed to average 30 stimuli. The average signals were displayed on an oscilloscope and traced out on an X-Y plotter. Stimuli for the VER consisted of 30 light flashes presented randomly at 5–10 s intervals from a diffuser screen in front of a Xenon flash tube situated 6 ft from the subject (0.49 Joules, 100 μs, light flash). Stimuli for the AER were 30, 1000 Hz or 360 Hz tones, duration 200 ms, volume 60 dB administered through head phones. The tones were presented randomly at 10–20 s intervals. Presentation of auditory and visual stimuli was controlled by tape-driven logic which also signalled to the computer and marked the physiograph chart paper used for recording skin conductance.

The visual and auditory evoked responses within the first 500 ms following stimulus onset were labelled as a sequence of positive and negative deflections from the vertex electrode according to the nomenclature of Davis *et al.* (1966). The sequence of deflections coincided with those described by Vaughan & Ritter (1970) (AER) and by Knott & Venables (1978) (VER) where $P_1 \equiv P_{IV}$, $N_1 \equiv$ P V and $P_2 \equiv$ P VI. Peak latencies were measured from stimulus onset to peak maximum (N_1) or minimum (P_1 and P_2). Mean ($\pm$ s.d.) pre-drug peak latencies (ms) for cannabis and placebo were as follows. AER: (P_1) 54.22 $\pm$ 8.82, (N_1) 115.47 $\pm$ 8.73, (P_2) 210.39 $\pm$ 28.04. VER: (P_1) 100.40 $\pm$ 19.83, (N_1) 143.71 $\pm$ 12.78, (P_2) 211.93 $\pm$ 20.57. Amplitude of N_1P_1 was measured from N_1 and P_1 maximum and minimum respectively and amplitude of N_1P_2 from N_1 and P_2 peak maximum and minimum respectively. The amplitudes were converted to μV using the calibration made at each session.

2. *Autonomic responses*

(a) Skin conductance level (SCL) and skin conductance response (SCR) were recorded on a Devices M19 physiograph, using a pre-amplifier sensitivity of 1 mm pen deflection equal to 500 ohms, from silver/silver chloride electrodes attached to the palmar surface of the first and second finger tips of the non-dominant hand. The electrode area was 0.7 cm^2, and an impressed current of 8 μA produced a current density of 11.4 μA cm^2.

SCL was read as the mean of 4 points of the skin resistance (K ohms) corresponding to each 30 s epoch used for heart rate sampling and converted to SCL μmhos by the formula

$$SC\ (\mu\ mhos) = \frac{1000}{SR\ (K\ ohms)}.$$

A range corrected version of the SCL data was also calculated as described by Lykken (1972). SCR was obtained from the GSRs occurring within the period 1–5 s from the onset of each stimulus (the tones used for obtaining the AER) using formula

$$SCR = \frac{1000}{SRL + GSR} - \frac{1000}{SRL}\ \mu\ mhos$$

where SRL is skin resistance (K ohms) observed at stimulus onset, and GSR is maximum height of the observed response from the running baseline. Trials to habituation were scored as the number of the last trial before three successive non-responses (criterion response 0.0526 μ mhos ≡ 0.5 K ohms change at 100 K ohms).

(b) Heart rate (HR) was recorded from two chest leads and an earth lead with output to the Devices M19 Physiograph. It was recorded continuously, and 30 or 60 s samples were selected from the records for analysis at appropriate times during the procedure of Experiments 1 and 2.

3. *Mood rating scales* Subjects rated themselves for tension, alertness, depression, detachment and anxiety on a scale where 100 was 'average', 0 'very much below average', and 200 'very much above average'. This rating scale has been used for other drugs and described previously (Ashton *et al.*, 1978b). In Experiment 1, an additional rating for intoxication or 'high' was measured similarly; in Experiment 2 the 'high' rating was the subject's self assessment on a 0–10 scale in which 0 was 'I don't feel at all stoned or high' and 10 was 'I feel as stoned or high as I have ever felt in my life'.

4. *Personality characteristics* Subjects in Experiment 1 completed an Eysenck Personality Inventory (EPI) (Eysenck & Eysenck, 1963) and were scored for Extraversion (E) and Neuroticism (N); subjects in Experiment 2 completed an Eysenck Personality Questionnaire (EPQ) (Eysenck & Eysenck, 1975) and were scored for E, N and Psychoticism (P). The subjects' scores were in the normal range for E and N; the score for P (mean 5.6 ± 4.3 compared to the normal range, 3.78 ± 3.09 for males and 2.63 ± 2.36 for females) was somewhat high in the 12 subjects who completed the EPQ, but this might be expected in a group of subjects who take drugs and volunteer for an experiment. One of the P scale items in the EPQ reads 'Would you take drugs which may have strange or dangerous effects?'

5. *Psychomotor performance*

(a) Reaction time (RT) was measured as described above during measurement of the CNV. Mean reaction time was taken as the mean of the 26 responses during each CNV series.

(b) Puzzle (Test Match Cricket, Acom Games). This consisted of 13 brightly coloured balls in a clear plastic box; by tilting the box, all the balls could be rolled into the 13 appropriate holes. The time taken to complete the puzzle was measured, as well as the HR and SCL response to its performance.

Procedure

For both experiments, the subject was seated by himself in a sound-proof, temperature-controlled (21°C) room with two-way communication via an intercom system with the experimenter, who could also see the subject through a one-way glass window. In each experiment the subject attended for one familiarisation session and two recording sessions, at least 1 week apart. Subjects were strongly instructed not to take cannabis for a week before each experimental session. During the recording sessions the subjects received 'blind' in random order one cigarette spiked with 2.5 mg or 10 mg Δ⁹THC (Experiment 1) or a placebo cigarette or one spiked with 8 mg Δ⁹THC (Experiment 2). During one of the recording sessions, the subjects in Experiment 1 performed a choice reaction time task (the results of which are not presented here) instead of a CNV task. While smoking the cigarettes, subjects in Experiment 1 (2.5 or 10 mg Δ⁹THC) were instructed to take one puff every 30 s, to inhale and to hold each inhalation for 8 s, and to continue until the cigarette was smoked to a mark just short of the filter. In Experiment 2 (8 mg Δ⁹THC or placebo), the number and rate of puffs taken were left to the subjects, although they were asked to inhale, to hold the smoke for a few seconds, and to smoke to the mark. It was suggested that these subjects should smoke to enjoy themselves. The number of puffs, time of each puff and duration of smoking were recorded. Details of the procedure in Experiments 1 and 2 are shown in Table 1. All experiments were conducted at the same time of day, in the afternoons.

Results

Experiment 1

CNV magnitude CNV magnitude with S_1–S_2 intervals of 2, 3 and 4 s were measured. The results of all these experiments were similar and are presented together. Analysis was carried out by means of a repeated measures factorial analysis of variance (Edwards,

Table 1 Experimental procedure

Activity	*Time*
Experiment 1 (n = 20)	
Personality inventory (EPI)	
CNV practice	−45 to −40 min
CNV pre-drug 1; mood rating	−30 to −25 min
CNV pre-drug 2; mood rating	−15 to −10 min
Subject smokes 2.5 mg or 10 mg Δ⁹THC in herbal cigarette (one puff every 30 s)	approx. 5–10 min
CNV post-drug 1; mood rating	+15 to +20 min
CNV post-drug 2; mood rating	+30 to +35 min
CNV post-drug 3; mood rating	+45 to +50 min
CNV post-drug 4; mood rating	+60 to +65 min
HR monitored continuously throughout experiment	
Experiment 2 (n = 12)	
Personality questionnaire (EPQ)	
Practice puzzle; mood rating	−50 to −40 min
Mood rating; puzzle; VER I	−30 to −18 min
Mood rating; puzzle; AER I*; SCR	−17 to − 9 min
Mood rating; puzzle; VER II	− 8 to − 3 min
Mood rating	− 2 to 0 min
Subject smokes 8 mg Δ⁹THC in herbal cigarette, or placebo (puffing rate determined by subject)	approx. 5–10 min
Mood rating	0 min
VER III	+ 2 to + 4 min
Mood rating; puzzle; AER II*; SCR	+ 5 to +12 min
Mood rating; puzzle; VER IV	+13 to +17 min
Mood rating; puzzle; AER III*; SCR	+18 to +25 min
Mood rating; puzzle; VER V	+26 to +31 min
HR, SCL monitored continuously throughout experiment	

* Order of 1000 Hz and 360 Hz tones randomised within sessions

1962) which took account of the influence of Δ⁹THC dosage (2.5 mg and 10 mg) and of personality factors (E and N scores) and their interactions on CNV magnitude measured repeatedly over time.

Figure 1 shows mean CNV magnitude across all subjects before and after drug treatment for the shortest and longest S_1–S_2 intervals. There was a slight increase in the magnitude of the first post-drug CNV with the longer S_1–S_2 interval ($P < 0.01$), but none of the other post-drug means differed significantly from the corresponding pre-drug means. Thus, with dosage and personality factors ignored, Δ⁹THC appeared to have little effect on CNV magnitude.

However, when account was taken of personality differences between subjects, highly significant drug effects emerged. Figure 2 shows the results for the 2 s S_1–S_2 interval when subjects were divided at the mean E score (13.11) on the EPI. In the relatively introverted subjects, who scored below this mean, there was an increase in CNV magnitude after Δ⁹THC while in the subjects who were relatively extraverted there was a decrease. The differences from the pre-drug to the post-drug (at 30 min) means, and between the two groups at post-drug (at 30 min) were significant for each sub-group ($P < 0.001$). Thus Δ⁹THC appeared to act as a stimulant of CNV magnitude to introverts but a depressant to the more extraverted subjects. Similar changes were observed in the CNVs obtained with longer S_1–S_2 intervals.

Highly significant differences in drug responses were also found when account was taken of neuroticism (N score on the EPI) and of drug dosage. The effects were similar in all CNVs but most marked in the CNVs obtained with the 4 s S_1–S_2 interval. These effects are shown in Figure 3. In subjects with N scores above the mean (9.44), the low dose of Δ⁹THC

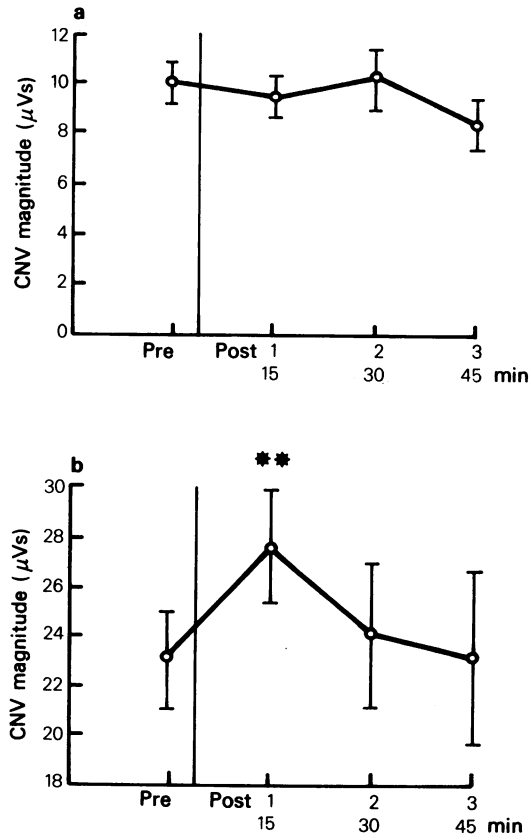

Figure 1 Mean ± s.e. mean CNV magnitude before and after Δ⁹THC (2.5 and 10 mg) for 20 subjects (a) 2 s S_1–S_2 interval (b) 4s S_1–S_2 interval.
Significant change in CNV magnitude from pre-drug level indicated by ** ($P < 0.01$, paired t-test).

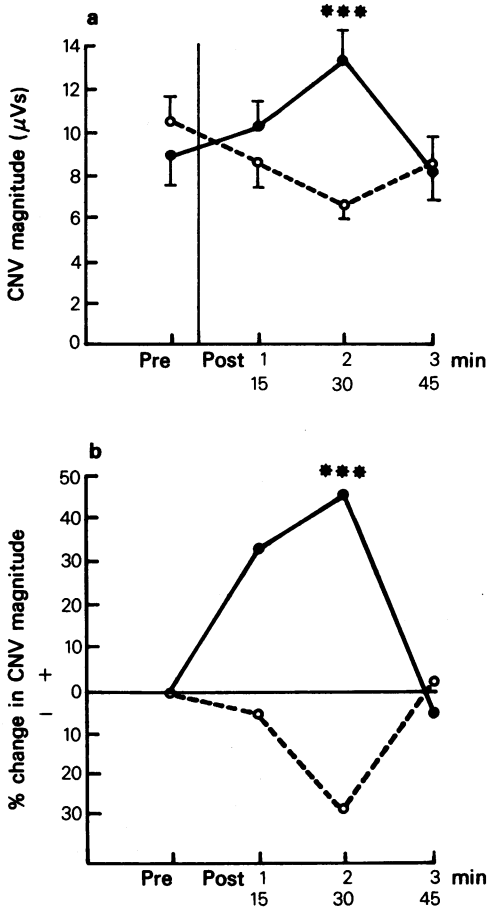

Figure 2 (a) Mean ± s.e. mean CNV magnitude (2 s S_1–S_2 interval) before and after Δ⁹THC (2.5 and 10 mg) for 20 subjects divided at mean E score (EPI score 13.11) into 10 introverts (●) and 10 extraverts (○).
(b) Percentage change in CNV magnitude from pre-drug level for the same subjects.
Significant differences between introvert and extraverts, and also between pre- and post-drug levels for each group indicated by *** ($P < 0.001$, paired t-test).

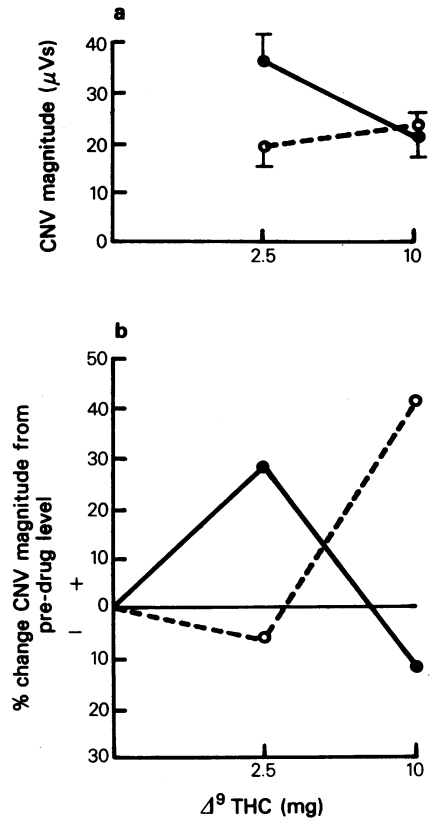

Figure 3 (a) Mean ± s.e. mean CNV magnitude (4 s S_1–S_2 interval) for post-drug CNV series 1–3 after 2.5 and 10 mg Δ⁹THC in subjects divided at mean N score (EPI score 9.44) into high N (●) and low N (○) groups. Ten subjects at each dose.
Dosage × neuroticism interaction is significant ($P < 0.003$, analysis of variance).
(b) Percentage change in CNV magnitude from pre-drug level for each dose in the same subjects. Dosage × neuroticism interaction is significant ($P < 0.001$, analysis of variance).

increased CNV magnitude while the high dose decreased it. By contrast, in subjects with N scores below the mean, the low dose of Δ⁹THC decreased CNV magnitude while the high dose increased it. The interaction dosage × neuroticism was significant ($P < 0.003$).

The interaction of dosage level with introversion was also significant ($P < 0.01$) for the 4 s S_1–S_2 interval (Figure 4). In introverts CNV magnitude increased 32.4% after the low dose compared to only 3.6% on the high dose, while in extraverts CNV size decreased by 9.3% on the low dose but increased 25.6% on the high dose.

As shown in Figures 3 and 4 the low dose of Δ⁹THC is associated with a stimulant effect on CNV magnitude in both introverted subjects and in those with high N scores, and a depressant effect in both extraverted subjects and those with low N scores. With the high dose of Δ⁹THC these effects are reversed. It might therefore be expected that a comparison between the small sub-group who were both introverted and anxious ('anxious introverts') and the small sub-group who were both extraverted and calm ('calm extraverts') would be even more differentiated. This was found to be the case. Figure 5 shows that on the low dose the anxious introverts had a large mean CNV size (over all three post-drug series) of 45.7 μVs compared with that of the calm extraverts

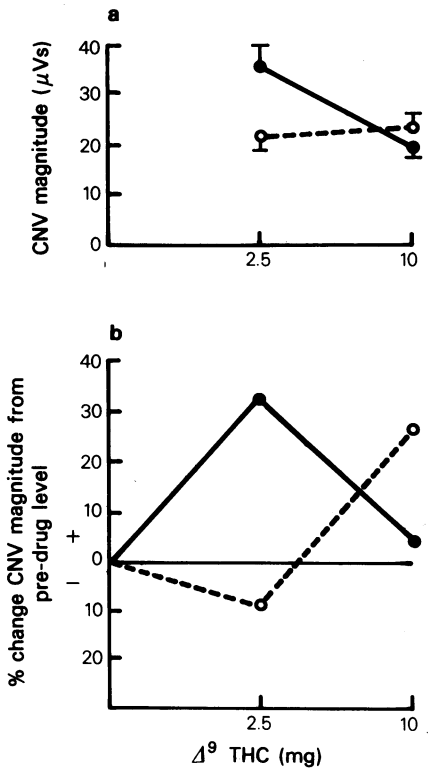

Figure 4 (a) Mean ± s.e. mean CNV magnitude (4 s S_1–S_2 interval) for post-drug CNV series 1–3 after 2.5 and 10 mg Δ^9THC in subjects divided at mean E score (○ extraverts, ● introverts), ten subjects at each dose. Dosage × introversion interaction is significant ($P < 0.01$, analysis of variance).
(b) Percentage change in CNV magnitude from pre-drug level for each dose in the same subjects. Dosage × introversion interaction is significant ($P < 0.001$, analysis of variance).

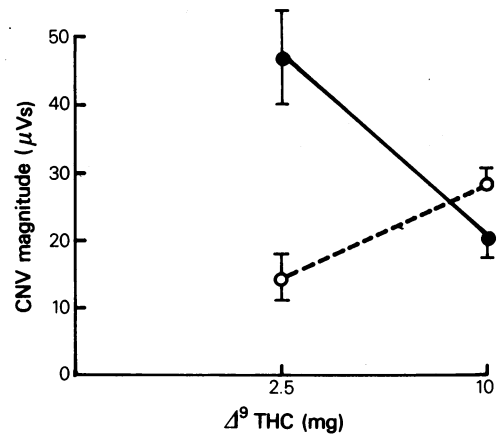

Figure 5 Mean ± s.e. mean CNV magnitude (4 s S_1–S_2 interval) for post-drug CNV series 1–3 after 2.5 and 10 mg Δ^9THC in anxious introverts (●) (N scores above the mean, 9.44 EPI, and E below the mean 13.11) and calm extraverts (○) (N scores below the mean and E above the mean). Six subjects received 2.5 mg, five subjects 10 mg. Differences between groups at both doses and within groups at the two doses are significant at $P < 0.05$ (paired t-tests).

which was only 14.7 μVs. This relationship was reversed on the high dose when the anxious introverts had a mean CNV size of only 20.3 μVs and the calm extraverts had increased their CNV magnitude to 28.0 μVs. The trend for the other two groups (calm introverts and anxious extraverts) was intermediate. The largest differential dose effect was that shown by the anxious introverts, although the overall N × E × Dosage interaction over these few subjects did not reach statistical significance.

All of the results indicate that the effects of different doses of Δ^9THC, which may be stimulant or depressant, depend strongly on the personality of the smoker, and if these aspects are overlooked, little or no drug or dosage effects may be appreciated.

Reaction time Overall, reaction times were slower after Δ^9THC when personality and dosage were ignored, but the changes were not significant. The greatest slowing of reaction time (11.3%) was associated with the higher (10 mg) dose and coincided with the maximum rating for Intoxication, but was not significant. When personality scores were considered in relation to dosage levels, it was found that the greatest slowing of reaction time (12.3%) occurred in the anxious introvert sub-group after the higher dose, while these subjects showed a 5–6% quickening of reaction time after the low dose. These changes, although not significant, were consistent with the finding that CNV magnitudes tended to be decreased by high dosage and increased by low dosage in the same subjects (Figure 5).

Mood rating scales The changes in mood ratings after both doses of Δ^9THC for all subjects are shown in Figure 6. The changes were generally maximal 30–45 min after smoking and were larger after the higher dose. The greatest change occurred in the intoxication ('high') scale after the 10 mg dose, but by 30 min all the mood ratings were significantly different from their pre-drug levels ($P < 0.05$ or less), except alertness on the lower dose and anxiety on the higher one. This is accounted for by some paradoxical increases in anxiety and alertness experienced by some subjects (see Figure 7). The change in ratings for intoxication, detachment and tension were also significantly different between the two dosage levels with t values of 3.00 or more ($n = 20$).

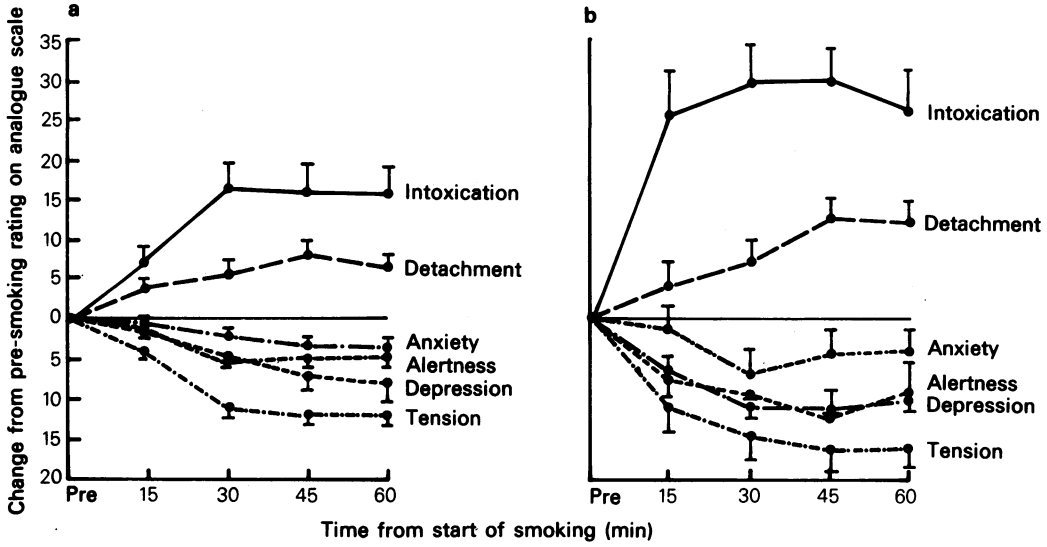

Figure 6 Mean ± s.e. mean changes in subjective mood ratings after (a) 2.5 mg Δ⁹THC (20 subjects) and (b) 10 mg Δ⁹THC (20 subjects). All ratings were significantly different from pre-drug levels ($P < 0.05$ or less, paired t-tests) by 30 min except alertness after 2.5 mg and anxiety after 10 mg. Differences between doses for intoxication, detachment and tension were significant at $P < 0.01$ or less (paired t-tests).

The extent and sometimes the direction of change in the mood ratings after Δ⁹THC was influenced by personality characteristics, as shown in Figure 7. On the intoxication scale the introverts generally produced greater increases than extraverts on both doses by 30 min. A differentiation was also seen between the calm and anxious sub-groups, those with lower N scores reporting more intoxication. Thus both calmness and introversion were associated with a greater 'high' and anxiety and extraversion with a lesser one, and at 30 min the calm introverts reported most intoxication while the anxious extraverts reported least. However the sub-groups are rather too small to support statistical analysis.

Anxiety was typically reduced by Δ⁹THC at both doses, although on the high dose the calm introverts reported a paradoxical increase in anxiety. Tension was also reduced in general and this effect was most marked in the calm extraverts on the higher dose. Alertness was reduced overall, but showed an increase in the anxious extraverts on the low dose. Depression decreased, especially on the higher dose and most markedly in the calm introverts. Detachment increased overall, the change being most marked in the anxious extraverts on the low dose and the calm introverts on the high dose.

Over all the six mood rating scales, the greatest effects of the 10 mg dose occurred in the calmer (low N score) subjects, whether introverted or extraverted (with the single exception of the paradoxical response of the calm introverts on anxiety and the weaker effects on the more anxious (high N score) subjects). A similar pattern was seen on the 2.5 mg dose, with a few exceptions. Thus inherent emotional arousal or excitability, as reflected in a high N score, appears to reduce the effects of Δ⁹THC on mood.

Heart rate Mean heart rates were measured for the period 1 min before and 1 min after each CNV and for 1 min during each task, and similarly before and after smoking and at the approximate mid-point of smoking. The mean results for all subjects for the two doses of Δ⁹THC are shown in Figure 8. Pre-drug heart rates were not significantly different between the two doses. The 2.5 mg dose of Δ⁹THC caused a maximum increase in mean heart rate of 10.7 beats/min, 1 min after the end of smoking, representing a 14.5% increase from the mean pre-smoking rate. Heart rate declined to pre-smoking levels by 45 min post-smoking. The 10 mg dose caused a maximum increase in mean heart rate of 25.66 beats/min a 34.8% increase, at 15 min after smoking. Heart rate then declined but did not fall to pre-smoking levels for about 2 h. Individual peak heart rate on the low dose approached 100 beats/min in two subjects while 120 beats/min was exceeded by two subjects on the high dose. No subjects reported spontaneously on their heart rate increases.

Experiment 2

In this experiment on different subjects, the effects

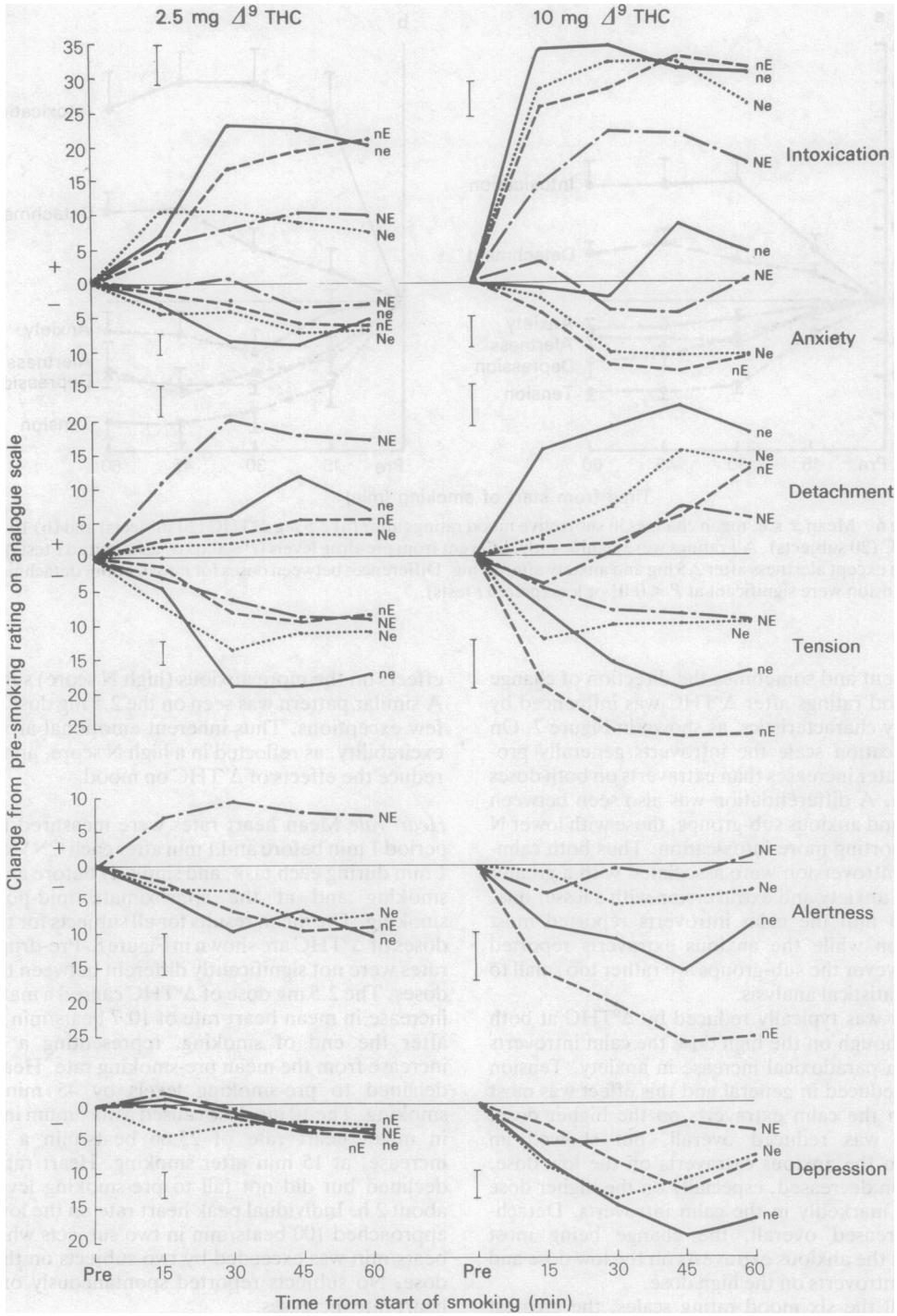

Figure 7 Mean changes in mood ratings after 2.5 mg and 10 mg Δ⁹THC in subjects divided into subgroups by personality scores: ne = low N, low E score; nE = low N, high E score; Ne = high N, low E score; NE = high N, high E score. Mean standard errors between bars; 20 subjects at each dose; 5 in each group.

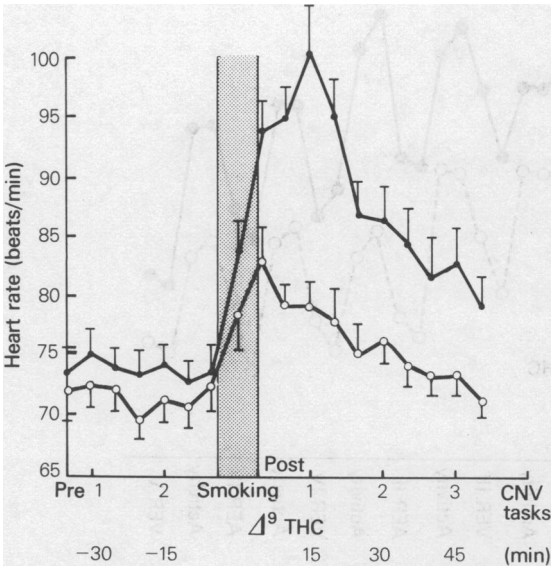

Figure 8 Mean ± s.e. mean heart rates before, during and after smoking cigarettes spiked with 2.5 mg Δ⁹THC (○) and 10 mg Δ⁹THC (●) in 20 subjects. Heart rate measured for 1 min before and after each CNV task and for 1 min during each task, and similarly before and after smoking and at the approximate mid point of smoking.

on some further variables of placebo herbal cigarettes were compared with those of cigarettes spiked with 8 mg Δ⁹THC. This dose was intermediate between the two doses used in Experiment 1, but smoking was not paced, the number and timing of puffs being left to the subjects. The results were analysed by means of paired 2-tailed *t*-tests and by correlation analysis.

Smoking style Significant differences in smoking styles were observed between the placebo and Δ⁹THC-spiked cigarettes (Table 2). With the Δ⁹THC cigarettes the mean total number of puffs was significantly smaller ($P < 0.001$) and the mean total smoking time significantly shorter ($P < 0.0001$) than with the placebo cigarettes.

Heart rate Figure 9 shows the heart rate changes during this experiment. Heart rate tended to rise while smoking both placebo and spiked cigarettes, but the rise was greater with the spiked cigarettes. The peak heart rate after Δ⁹THC was observed at 13 min after the end of smoking and amounted to a mean rise of 12.6 beats/min, while the heart rate 13 min after placebo smoking had dropped below the pre-smoking value. The pre- to post-drug difference between Δ⁹THC and placebo was highly significant ($P < 0.0001$). The fact that the rise in heart rate after 8 mg Δ⁹THC in this experiment was closer to that observed after 2.5 mg than that after 10 mg in Experiment 1 was probably due to the more natural smoking in Experiment 2, which may have led to the subjects inhaling a lesser proportion of the spiked dose. Heart rate reactivity to the task demands of the experiment was not significantly affected by Δ⁹THC.

Mood rating scales The results of the 'high' rating scale are shown in Figure 10. It was interesting to note a considerable placebo effect on this variable; however, the 'high' ratings were significantly greater after Δ⁹THC than after placebo ($P < 0.0001$). Tension and alertness also decreased after 8 mg Δ⁹THC to a similar extent as in Experiment 1, and at 30 min post-smoking the ratings were significantly different from the pre-drug levels ($P < 0.05$), whilst after placebo there was no significnat effect at 30 min. Detachment, anxiety and depression were not significantly altered by either drug or placebo in this experiment. Differences in the effects of Δ⁹THC on the rating scales between Experiments 1 and 2 were probably largely due to differences in duration and procedure, the subjects in Experiment 2 being more intensively involved in task activity but for a shorter time post-drug.

Skin conductance There was no significant overall differences between drug and placebo in pre- or post-smoking values for SCL or SCR. However, the habituation rate to tone was significantly quickened by Δ⁹THC 20 min post-smoking compared with placebo ($P < 0.05$). In addition there was a highly significant correlation between the basal (pre-drug) level of SCR and the change in SCR after Δ⁹THC (see correlations, below).

Psychomotor performance The time taken to complete the puzzle was not significantly altered by drug

Table 2 Smoking style in ten subjects smoking placebo cigarettes and cigarettes spiked with 8 mg Δ⁹THC

Variable	*Δ⁹THC*	*s.d.*	*Placebo*	*s.d.*	P *(paired* t-*test)* d.f. = 9
Mean total puffs	12.50	2.70	16.50	4.20	<0.001
Mean total time smoking (min)	5.35	0.87	6.97	1.20	<0.0001

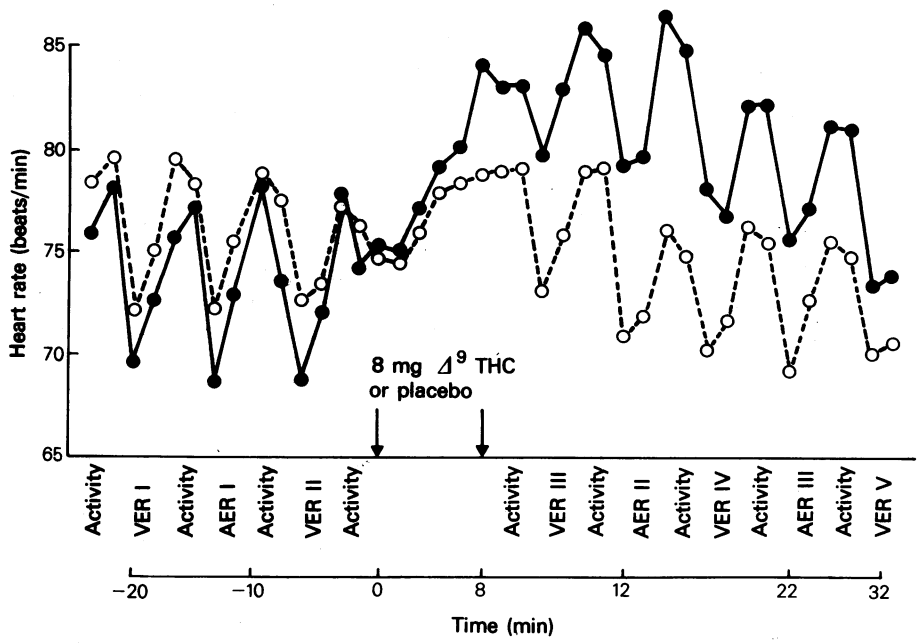

Figure 9 Mean heart rate for eleven subjects, before, during and after smoking placebo cigarettes (○) and cigarettes spiked with 8 mg Δ⁹THC (●). Mean pre- to post-drug difference in heart rate between placebo and Δ⁹THC significant ($P < 0.0001$, paired t-test).

or placebo. However, the variance was markedly increased after Δ⁹THC (mean time to complete puzzle pre-drug = 26.0 ± 2.21 s; 15 min post drug = 44.5 ± 11.99 s).

Cortical evoked responses There were no differences between drug and placebo in the amplitude or latency of any of the components of the AER. However, in the VER, the amplitude of the N_1P_1 component was reduced and the latency of N_1 was prolonged after Δ⁹THC compared with placebo ($P < 0.013$ and < 0.044 respectively). The latency of the P_1 component was also prolonged 30 min after Δ⁹THC ($P < 0.05$) but not overall. These changes are shown in Figure 11.

Correlations Figure 12 shows the correlation between basal skin conductance reactivity (SCR) to performance of the puzzle task and change in SCR (post- to pre-drug). Δ⁹THC produced an increase in SCR in subjects with low basal reactivity and a decrease in SCR in those with a high basal reactivity ($r_1 = -0.96$, $P < 0.001$). By contrast this effect was non significant for placebo ($r_2 = -0.59$) and the difference between Δ⁹THC and placebo for these correlation coefficients was significant (using z transformation of r_1 and r_2; c = 2.308; r_1 v r_2, $P < 0.03$). It is also noteworthy that pre- v post-drug correlations were highly significant ($P < 0.01$) for both Δ⁹THC ($r = +0.866$) and

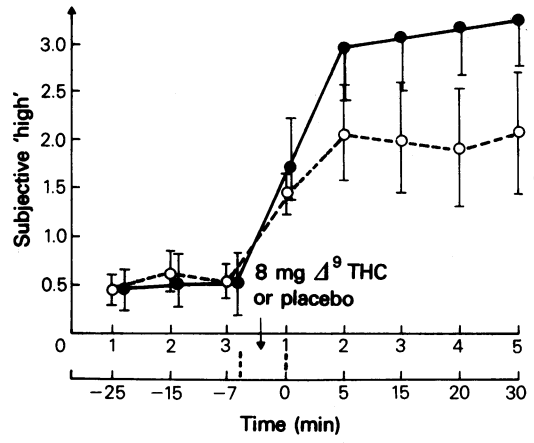

Figure 10 Mean ± s.e. mean subjective 'high' ratings oin scale from 0–10 in eleven subjects before and after smoking placebo cigarettes (○) and cigarettes spiked with 8 mg Δ⁹THC (●). Post-smoking overall high ratings (5–30 min) significantly greater after Δ⁹THC than after placebo ($P < 0.0001$, paired t-test).

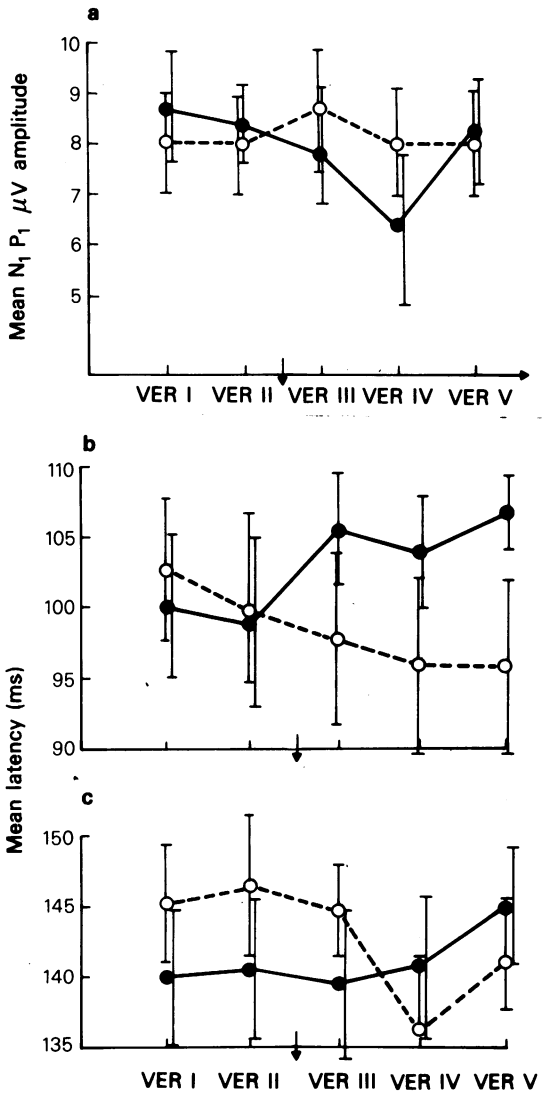

Figure 11 Visual evoked response changes (mean ± s.e. mean) in 12 subjects after smoking placebo cigarettes (○) and cigarettes spiked with 8 mg Δ⁹THC (●). The arrow indicates the time at which the cigarettes were smoked.

(a) N_1P_1 amplitude, change post-drug significantly different between placebo and Δ⁹THC ($P < 0.01$, paired t-test)

(b) P_1 latency; latency at VER IV (30 min post-drug) significantly different between placebo and Δ⁹THC ($P < 0.05$, paired t-test) but not overall.

(c) N_1 latency; change post-drug significantly different between placebo and Δ⁹THC ($P < 0.05$, paired t-test).

placebo ($r = +0.749$). This indicates that SCR measurement was reliable and thus obviates the possibility that significant negative pre-drug with post-minus pre-drug correlations could be due to variability between successive observations. (If this were the case, cannabis could be viewed as simply increasing the lability of the SCR). This effect appeared to be also related to subjective 'high' rating: subjects with a low basal SCR, who were stimulated by Δ⁹THC, experienced a greater 'high' than those with a high basal SCR which was depressed by Δ⁹THC although the correlation did not reach significance.

None of the personality characteristics, extraversion, neuroticism or psychoticism, correlated with 'high' ratings after Δ⁹THC or placebo in this experiment. However, tension was significantly correlated with smoking behaviour (Table 3), higher pre-smoking tension predicting a greater number of puffs of Δ⁹THC spiked-cigarettes ($r = 0.75$; $P < 0.05$) and a longer total time smoking both spiked ($r = 0.63$, $P < 0.05$) and placebo ($r = 0.85$, $P < 0.05$) cigarettes. Reduction in tension post-smoking correlated significantly with total time smoking Δ⁹THC ($r = -0.63$, $P < 0.05$), but not placebo. It is interesting that total time smoking was a highly significant discriminator between Δ⁹THC and placebo ($P < 0.0001$, Table 2). Thus a greater reduction in tension was associated with a greater 'high'.

Self-titration in Δ⁹THC smoking The subjects in Experiment 2 were instructed to smoke to enjoy the cigarettes, which they thought would contain smaller or larger doses of Δ⁹THC, and they were presumably smoking with the expectation of obtaining a 'high'. In this setting, the measures which best discriminated between 8 mg Δ⁹THC and placebo were smoking behaviour (shorter total time smoking Δ⁹THC; $P < 0.0001$, and fewer puffs with Δ⁹THC; $P < 0.0001$, Table 2) and elevation of heart rate (greater elevation after Δ⁹THC; $P < 0.0001$, Figure 9). The change in smoking behaviour suggests an attempt at self-titration for effective doses of Δ⁹THC by the placebo smokers. It appears that subjects could detect at some unconscious level that they were smoking inactive cigarettes and reacted by an increased puffing rate and longer duration of smoking.

Immediately post-smoking, there was no significant difference in 'high' ratings between drug and placebo, though for both there was a significant rise from the pre-smoking level ($P < 0.02$). Thus the curious situation arose that while the subjects were not consciously aware of the difference between drug and placebo, as shown by their subjective ratings, external observation of their smoking behaviour was an absolute discriminator between drug and placebo. This finding seems to be unique in the cannabis literature, largely because most studies have emphasised strict experimental control of smoking rate in order to standardise dosage.

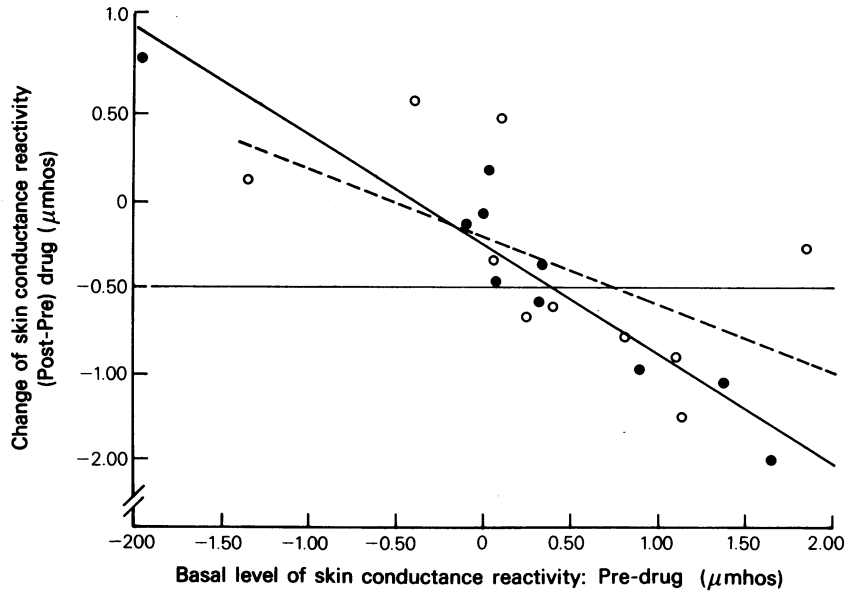

Figure 12 Correlation between change in skin conductance reactivity (SCR) and basal (pre-drug) SCR after 8 mg Δ^9THC (●) and placebo (○) in ten subjects. For Δ^9THC, $r = -0.95$, $P < 0.001$; for placebo, $r = -0.59$, P = NS. (Regression equations: Δ^9THC y = −0.641 × +0.254; placebo y = −0.394 × +0.290).

It seemed possible that heart rate changes could have supplied an internal cue that caused subjects to modify their smoking behaviour. In a subsidiary experiment, the same dose of Δ^9THC (8 mg) was administered either in lettuce leaf cigarettes (Bravo, containing no nicotine, 19 subjects) or in cigarettes with an estimated nicotine yield of 1 mg (Guards, 22 subjects). The subjects knew they were likely to receive Δ^9THC but thought it would be contained in ordinary tobacco cigarettes. The smokers of the nicotine cigarettes showed a greater heart rate elevation than those of the nicotine-free cigarettes (Figure 13). Furthermore, the nicotine smokers took significantly fewer puffs per cigarette (Table 4) and probably obtained less Δ^9THC than the nicotine-free smokers, since they subsequently reported a lesser 'high'. It seems plausible that the greater elevation of heart rate due to the nicotine acted as a false internal cue for estimating Δ^9THC ingestion and led to a downward titration of dose. A degree of self-titration for nicotine during cigarette smoking has often been observed (Ashton, Stepney & Thompson, 1979; Russell *et al.*, 1975) and for smokers taking cannabis with tobacco, as is usual, interesting interactions could arise between self-titration for nicotine and/or cannabis.

However, although heart rate elevation may signal Δ^9THC dosage while smoking, it does not appear to be a necessary concomitant of the subjective 'high'. In the present experiments, heart rate peaked at 1 min after 2.5 mg Δ^9THC, at 13 min after 8 mg and at 15 min after 10 mg and thereafter declined, while 'high' ratings were still on an elevated plateau at 60 min after smoking. Furthermore, Sulkowski, Vachon & Rich (1977) reported that the β-adrenergic receptor blocking drug propranolol can abolish cannabis-induced tachycardia while leaving the subjective 'high' relatively intact.

Discussion

The results of both experiments show that, unless the characteristics of the individual subjects are taken into account, very little overall drug effect, apart from a rise in heart rate and a subjective 'high' may be apparent after pharmacologically active doses of Δ^9THC, in spite of the fact that it is a potent psychotropic agent with actions on many body systems. In some subjects or settings even the 'high' may not be demonstrable, since a considerable 'high' can be obtained from placebo.

The extent of the subjective 'high' produced by Δ^9THC appears to depend on the personality of the taker, including both E and N scores (Figures 2–4). In Experiment 1, both introversion (low E score) and calmness (low N score) were associated with a greater increase in intoxication after both doses (2.5 and 10 mg). Personality characteristics also influenced the other mood ratings. In general the greater subjective

Table 3 Correlations (r) between smoking style and tension rating before and after smoking placebo and Δ⁹THC-spiked cigarettes. (* $P < 0.05$; ** $P < 0.01$) ($n = 12$)

	Tension (pre-drug)	*Tension (post-pre-drug)*
Total puffs Δ⁹THC	0.75*	−0.08
Total puffs placebo	0.57	0.39
Total time smoking Δ⁹THC	0.63*	−0.63*
Total time smoking placebo	0.85**	0.02

effects of Δ⁹THC were experienced by the calmer subjects whether they were introverted or extraverted. By contrast, anxious subjects (high N score) appeared to put up a certain resistance to many effects of Δ⁹THC; these subjects not only became less intoxicated but also showed less decrease in tension, alertness and depression than calm subjects. The small subgroup of neurotic extraverts (high N and E scores) sometimes responded to Δ⁹THC in unpredictable ways. This was most marked after the low dose (2.5 mg) after which, in contrast to all other subjects, they reported definite increases in detachment and in alertness. Such responses would be consistent with other observations on subjects in this personality quadrant, described by Eysenck (1967) in terms of hysteria and psychopathy.

The influence of personality on the response to cannabis and to many other drugs administered experimentally is well recognised (Eysenck, 1967). For drugs which are usually self administered, such as nicotine in smoking, the dose of the drug taken (presumably to achieve some optimal effect) is also influenced by personality (Ashton *et al.*, 1974). In Experiment 1 the rate of smoking was controlled and it is possible that subjects with different E and N scores would have self-administered different doses in a more natural setting. Thus the discrepancies between the subjective effects of Δ⁹THC according to personality may have been to some degree artificially induced by the conditions of the experiment. In Experiment 2 the smoking was natural, but there were not enough subjects to separate them into personality subgroups. Nevertheless it is interesting that there were significant positive correlations between decrease of tension and smoking style (Table 3).

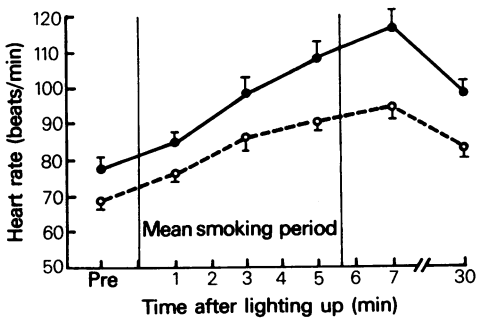

Figure 13 Mean ± s.e. mean heart rates before, during and after smoking nicotine-free cigarettes (Bravo, 19 subjects, O) and cigarettes with a nicotine yield of 1 mg (Guards, 22 subjects ●), both cigarettes spiked with 8 mg Δ⁹THC. Percentage increase in heart rate from pre-smoking levels to peak was significantly greater for Guards than Bravo cigarettes ($P < 0.005$, t-test).

The present experiments provide evidence of stimulant as well as depressant effects of Δ⁹THC on CNV magnitude and on SCR. As shown in Figures 3 and 4, CNV magnitude was increased after 2.5 mg Δ⁹THC in introverted subjects and in those with high N scores, and after 10 mg in extraverted subjects and those with low N scores. Similar increases in CNV magnitude have been shown to occur after central stimulant drugs such as caffeine, methamphetamine, pemoline, low doses of nicotine and LSD (Ashton *et al.*, 1974, 1980; Kopell *et al.*, 1974; Walter, 1964). Conversely, CNV magnitude was decreased after 2.5 mg Δ⁹THC in extraverted subjects and in those with low N scores, and after 10 mg in introverted subjects and in those with high N scores. Such decreases in CNV magnitude occur after central depressant drugs such as ethanol, benzodiazepines, barbiturates, chlorpromazine and high doses of nicotine (Ashton *et al.*, 1974, 1980; Kopell, Tinklenberg & Hollister, 1972; Kopell *et al.*, 1974; Halblitz & Borda, 1973; Tecce, Cole & Savignano-Bowman, 1975). The stimulant effect of Δ⁹THC on CNV magnitude may possibly reflect an increase in sensory traffic into the reticular activating system, which is known to be involved in the genesis of the CNV (Rebert, 1972). A few subjects did spontaneously remark on a heightened awareness of the electrodes attached to the skin after smoking but they apparently did not rate this as part of the 'high' and there was no correlation between CNV magnitude and intoxication ratings. The depressant effect of Δ⁹THC on CNV magnitude could be due to dose and personality-related actions in the opposite direction on the same brain system or to separate depressant effects on different systems. Biphasic dose-related

Table 4 Mean duration of smoking and mean number of puffs taken to smoke non-nicotine (Bravo) or nicotine (Guards) cigarettes spiked with 8 mg Δ^9THC

Cigarette	n	*Duration of smoking*			*Puffs per cigarette*		
		Mean	*s.e. mean*	P	*Mean*	*s.e. mean*	P
Bravo (no nicotine)	19	5 min 36.8 s	15.5 s	NS	18.53	1.15	<0.001
Guards 1 mg nicotine yield	22	5 min 52.2 s	13.4 s		13.04	0.64	
Total	41	5 min 46.3 s	13.9 s		15.61	0.84	

effects of marihuana on CNV magnitude have been reported previously by Braden, Stillman & Wyatt (1974), and the direction of CNV response to nicotine is influenced by both dose and personality (Ashton *et al.*, 1974, 1980; Eysenck & O'Connor, 1979).

Skin conductance reactivity also showed both stimulant and depressant effects, and these were dependent on the starting state. As illustrated in Figure 12, Δ^9THC, smoked naturally, acted as a stimulant for individuals with low basal reactivity and as a depressant for individuals with a high basal reactivity. This response was not seen with placebo and suggests that Δ^9THC exerted a 'normalising' effect on the excitation level for this measure. It has been postulated (Berlyne, 1971) that activities which lead to a shift in arousal towards an 'optimum' level are rewarding, and it seems likely that this homeostatic principle may be evoked for the action of Δ^9THC on SCR. The effect may be analogous with the normalising effects of nicotine cigarette smoking but not of sham cigarette smoking on spontaneous skin conductance fluctuations, an electrodermal measure of excitation-inhibition balance (Mangan & Golding, 1978).

The significant increase in electrodermal habituation rate to tones at 20 min after 8 mg Δ^9THC, when the 'high' reached its maximum, appears to be an original finding. It may be that after Δ^9THC smoking inhibition rapidly sets in for monotonous irrelevant stimuli (60 dB tones). In real life situations, such as car driving, such an action of cannabis could lead to a loss of vigilance when driving becomes monotonous, and coupled with increased distractibility, be a cause of accidents. It was found that after Δ^9THC, excitation to the first stimulus remained unaffected whilst subsequent stimuli rapidly habituated; such a state would tend to increase distractibility.

The results of the visual and auditory evoked responses are consistent with the conclusions of other workers (Roth *et al.*, 1973; Low, Klonoff & Marcus, 1973; Lewis *et al.*, 1973) that whereas most drugs which exert an action on evoked responses affect amplitude, by contrast Δ^9THC affects mainly latency. In the present experiment, the latency of the visual N_1 and P_1 components was increased and the amplitude of the visual N_1P_1 component was reduced (Figure 11). Evoked response latency has been inversely correlated with mental efficiency, for example I.Q. (Hendrickson & Hendrickson, unpublished observation; Ertl & Schafer, 1969; Weinberg, 1969) and age (Goodin *et al.*, 1978; Olrich *et al.*, 1978). It is possible that the longer evoked response latencies after Δ^9THC are the result of depressant effects on brain activity leading to reduced 'efficiency'.

The close interrelations between subjective, autonomic and cortical evoked potential responses to Δ^9THC are perhaps not surprising in view of the finding (McIsaac *et al.*, 1971) that ^{14}C-labelled Δ^9THC is distributed in high concentrations to the hippocampus and amygdala of the monkey brain. In this region the mechanisms for intellectual and emotional functions are almost inextricably intertwined with those for autonomic and other somatic responses. Other drugs with actions in these areas would be expected to exhibit similar characteristics. The finding that both autonomic effects and effects on mental performance of the ACTH 4–10 fragment are personality-dependent (Breier, Kain & Konzett, 1979) provides a further example which probably applies to many psychoactive drugs. The interactions between dosage, personality and starting state with drug effects are important in experimental design, statistical analysis and clinical practice when such drugs are used.

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